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A Comprehensive Review on Oral Cancer Therapies and Drugs

[1]Rakesh Tiwle*, [2]Swati Lilhare
[1]Agrasen College of Pharmacy, Dagania, Gunderdehi, Balod, Chhattisgarh
[2]Institute of pharmaceutical science and research, Dongariya, Balaghat, Madhya Pradesh

****Corresponding Author***
Email Id: rakesh_tiwle@rediffmail.com

ABSTRACT

Buccal Mucosa is the commonest oral cavity cancer in India. It is most common and challenging malignancies of the head and neck region. Oral cancer is a hazardous Recent Innovations in Oral Cancer early detection and Cure modalities for cancer especially head and neck cancer depend on the TNM staging assessment, metastasis, Biopsy results, radiotherapy, chemotherapy. It is well known fact that Prompt detection of head and neck squamous cell carcinoma is vital to successful management. In this review article we are focus on instantaneous intraoral dispersible technologies as novel drug delivery systems because; they have outstanding advantages over the traditional oral and parenteral routes of drug administration.

Keywords: *Oral cancer, Squamous cell carcinoma, Tobacco smoking, Dispersible film.*

INTRODUCTION

Cancer is defined as a series of disease caused by persistent tissue injury and host-environment interactions. Oral squamous cell carcinoma ranks as the 15th most common cancer around all over the world out of these 10th most frequent in the males.[1] Incidence rates are high among males. Although mortality from oral cancer it has decreased in the past few decades, Oral cavity cancer is a major global health issue or heath problem in human being. oral cancer is estimated to be the 3rd most common malignancy after cancer of the cervix and stomach. It is a type of malignant neoplasia started through lip or oral cavity. Oral cancer is two to three times more prevalent in men than women in most ethnic groups, because in the mouth or dental area. [2] In all over worldwide report of the cancers of all regions of the oral or dental cavity and pharynx are grouped and collectively represent the many most common cancer in the world[3]. Oral cancer is the eleventh most common cancer in the world.[4] There is a wide geographical distribution in the incidence of oral cancer, with approximately two-thirds of patients in the developing countries of Southeast Asia, Eastern Europe and Latin America[5] In India, the gingival–buccal complex Human papillomavirus (HPV) is widely accepted as a cause the factor for cancer arising in the lymphoepithelium of the oropharynx its presence in lesions of oral cavity is less common; and its contribution to oral cancer development is uncertain[6]. There has been significant interest in the development of modified.[7] release oral dosage forms because oral delivery market holds approximately 52% of the market in the overall drug delivery market. But there are some commonly associated problems with oral administration of drugs like minimizing the risk of partial loss of active ingredients due to tablet or capsule crushing or imprecise liquid administration which leads to dosage inaccuracy and drug therapy overdosing or inefficiency[8]. A large-scale epidemiological survey of oral cancer and precancer was started in 1966 in several areas of India. While some oral cancer survivors may receive dental hygiene treatment within a cancer centre, it is likely that many oral cancer survivors will receive their dental hygiene therapy at

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a private dental office. Dental hygienists must be aware of the types of treatment that oral cancer patients receive and be cognizant of the effects that these treatments may induce. [9]

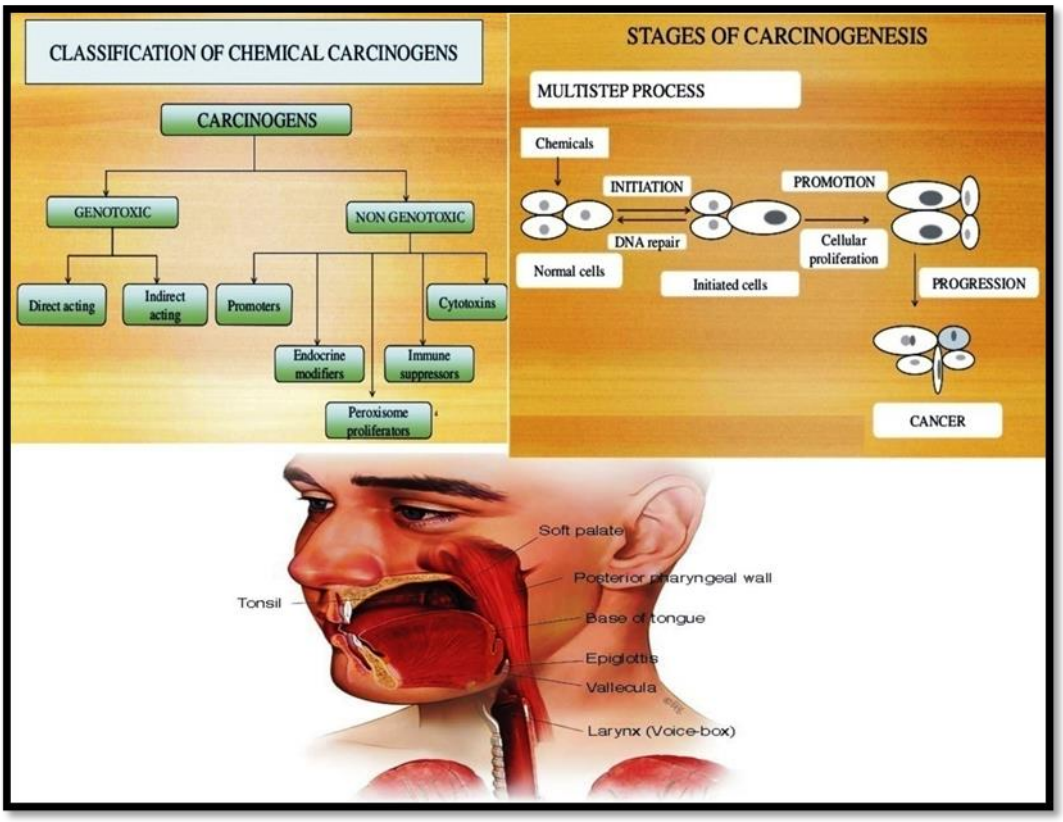

Fig. 1. Classification and Anatomy of oral Cancer

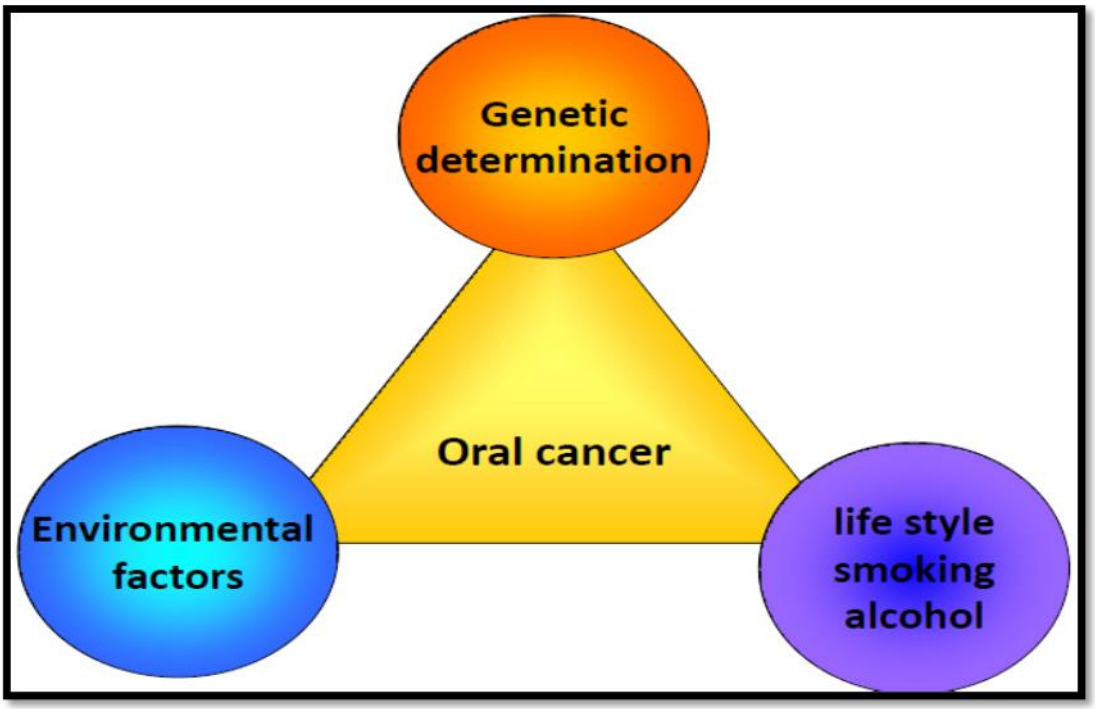

Fig. 2. Representation of Oral Cancer

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Scenario of Oral Cancer

1) In the year 2004 world health report accounts about 7.1 million deaths in the year 2003 it was estimated that overall numbers of new cases of oral cancer will arises by 60% in the coming next 20 years.
2) Cancer is the most common worldwide and having a 8th position and highly in men.

The preliminary survey was divided into 2 phases:

(a) Phase 1: The project was a cross-sectional field survey undertaken in 1966 -67 covering five districts in four states of India, each chosen for the particular tobacco smoking and chewing habits of the inhabitants.[11] The objective was to determine the prevalence of oral cavity cancer precancerous lesions and their association with tobacco and smoke usage. The results of this baseline survey, covering 50915 rural individuals, were published in 1969 [12]

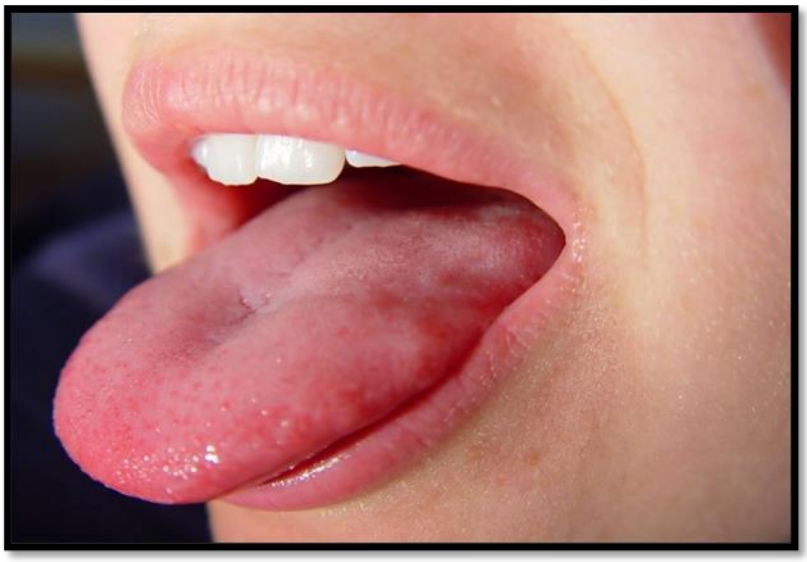

Fig. 3. Overview of Tongue

(b) Phase 2: The project was a 10-year follow-up of 60/o of the study of population. Two of the original districts were not included in this phase because very few precancerous lesions were detected there. A comprehensive report of this follow-up.[13]

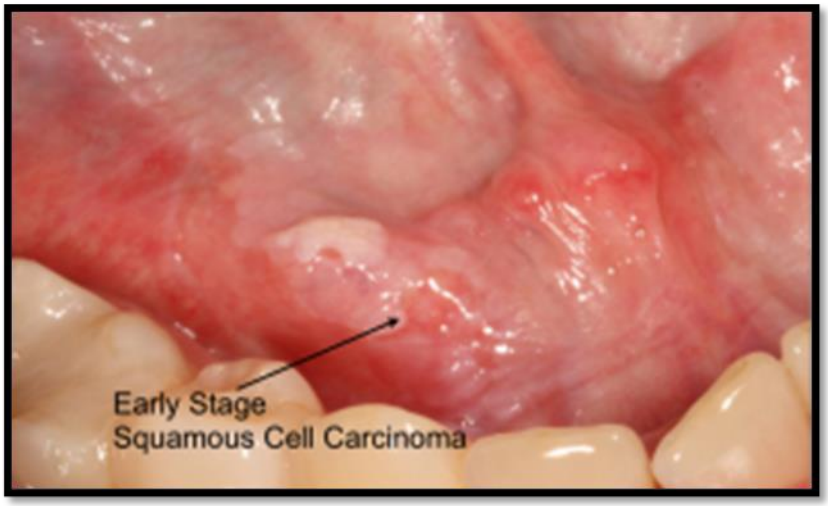

Fig. 4 Overview of Mouth Cavity

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Etiology of Oral Cancer

- Tobacco
- Alcohol
- Exposure to sun light
- Diet and nutrition
- Fungal infection.

Epidermology

Oral cancer most commonly occurs in middle-aged and older individuals, although a disturbing number of these malignancies is also being documented in younger adults in recent years.[14] From anepidemiological and oral oncology perspective, "oral cancer" can be divided into three types: carcinomas of the oral cavity proper, carcinomas of the lip vermilion, and carcinomas arising in the oropharynx. Intraoral and oropharyngeal tumors are more common among men than women, with a male:female ratio of over 2:1. [15]

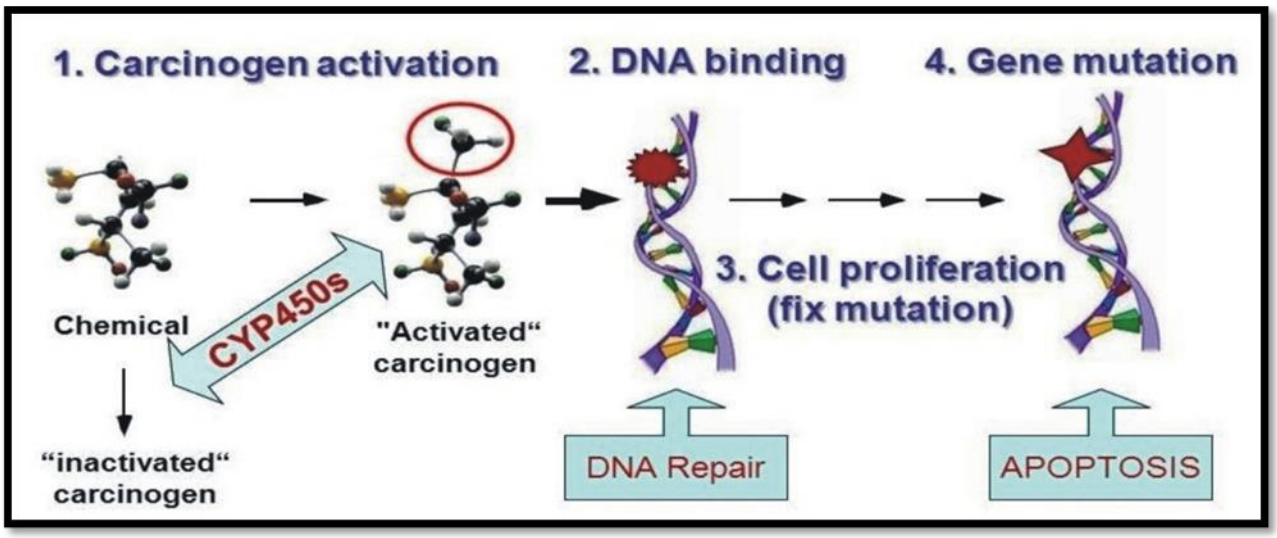

Fig. 4 Mechanism of Carcinogenesis Cancer

RISK FACTORS

Tobacco and Alcohol

The major risk factors associated with oral cancer are tobacco use, in any available forms, and highly amount of alcohol consumption (people who drink alcohol to five to eight drinks per day with one drink containing 1.5 oz or 10-15 g of alcohol) [16] The combined effects of alcohol and tobacco smoking have been shown to be synergistic. Of interest, a recent study showed that drinking is inversely associated with oral cancer in non-smoking betel quid non-chewing tobacco individuals [17]. The mechanisms of oral carcinogenesis is induced by the tobacco and smoking constituents [18]. Be-sides, the risk for oral cancer is 35% lower in people who quit smoking four years ago than those who contineusly smoking, and not higher in persons with no smoking antecedents for over 20 years when compared with people who have never smoked.[19] An environment with cigarette smoke is also risky; the risk for oral cancer is 87% higher in those who never smoked, but were exposed to an environment with cigarette smoke (involuntary smoking) compared with those who never smoked and not have been exposed [20]

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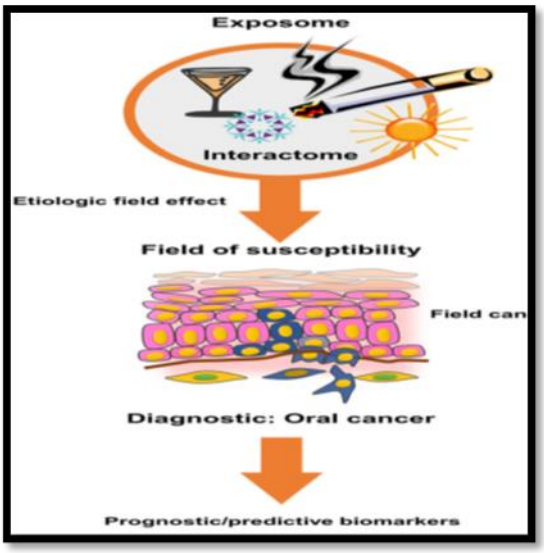

Fig. 5. Diagnosis of Oral Cancer

Alcohol

Alcohol (ethanol) can act as a both locally and systemically risk factor: increased permeability of oral mucosa, dissolve in a lipids components of the epithelium, causing epithelial atrophy and interference in DNA synthesis and repair; it also has genotoxicity and mutagenic effects, causing decreased in salivary flow, affects the liver's ability to deal with toxic or potentially carcinogenic compounds, and their chronic use is associated with an impairment of innate and acquired immunity, resulting in increased susceptibility to infections and neoplasms[20].

Fig. 6. Tobacco and alcohol

Age and Family History of Cancer

Age indicates a temporal component in the biochemical and biophysical processes of cells that allow malignant transformation or the reduction of the immune system competence [21]. Also, family history of oral cancer work plays an important role and is considered a risk factor. However, more studies are necessary to elucidate which molecules and genes are responsible for oral cancer susceptibility in families. Family history of oral cancer is mostly associated with an onset of the disease at an early age (about 45 years old) [22]

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Areca Nut Chewing

Areca nut which are regarded as a type 1 carcinogen is chewed raw, dried, or roasted, or as part of betel quid by millions of people in Asia; its use is spreading across the Pacific, as well as in emigrant Asian communities worldwide. Cheap, prepackaged areca nut products, such as pan masala, and tobacco are of recent concern, especially among youth. The inclusion of tobacco in the betel quid adds considerably to the carcinogenicity [23]

Fig. 7. Areca Nut

Table 1. GLOBOCAN cancer incidence and mortality, all ages, both sexes by population

Population	Incidence/ numbers	Crude rate	ASR (W)	Accumulative Risk
WHO African Region (AFRO	13,484	1.5	2.7	0.30
WHO Americas Region (PAHO)	49,200	5.2	4.1	0.48
WHO East Mediterranean Region (EMRO)	20,681	3.3	4.6	0.52
WHO, Europe	65,933	7.3	4.6	0.53
WHO South-East Asia Region (SEARO)	103,464	5.6	6.4	0.73
WHO Western Pacific Region (WPRO)	47,524	2.6	2.0	0.22
UNDPVery High Human Development	92,338	8.0	4.8	0.54
UNDP Low Human Development	40,954	3.1	5.2	0.59
GLOBOCAN More Developed	100,823	8.7	4.7	0.54

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Regions*				
GLOBOCAN Less Developed Regions*	199,550	3.4	3.7	0.42

Orally Disintegration Film

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in recent [24]. Orally disintegrating films (ODFs), when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form.[25]

The administration of ODFs has numerous advantages and some of them are as follows

1) Easy transportation.
2) Ease of swallowing for geriatrics and pediatrics.
3) Convenient and accurate dosing.
4) No need of water for administration.
5) Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
6) Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability.[26]

Mouth dissolving film (MDF) is new drug delivery system for the oral delivery of the drugs. Mouth dissolving film are the most advanced forms of oral solid dosage forms due to more flexibility and comfort. MDFs are strip type preparations with active molecules dissolved or dispersed in film forming materials.[27]

Fig. 8. Dispersible film

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Oro-Pharyngeal Cancer

Oro-pharyngeal cancer is significant component of the global burden of cancer. Tobacco and alcohol are the major risk factors for oral cancer.[28] It has been difficult to distinguish the separate effects of these agents, however, since drinkers of alcoholic beverage tend to be users of tobacco, and vice versa. Large scale epidemiological investigations have documented a synergistic effect of tobacco and excessive use of alcohol on the occurrence of oro-pharyngeal cancer. The population-attributable risks of smoking and alcohol consumption have been estimated to 80% for males, 61% for females, and 74% overall.[29]. The evidence that smokeless and tobacco causes oral cancer was confirmed recently by the International Agency for Research on Cancer.[30]Moreover, studies have shown that heavy intake of alcoholic beverages is associated with nutrient deficiency, which appears to contribute independently to oral carcinogenesis oral cancer. [31] Dietary factors have been thought to account for about 30% of cancers in Western countries [World Health Organization. 2005], making diet second only to tobacco as a preventable cause of cancer. The contribution of diet to cancer risk in developing countries has been considered to be lower, perhaps around 20%.[32]

The WHO Platforms for Prevention and Control of Cancer

Cancer is one of the major threats to public health in the developed world and increasingly in the developing world. Cancer is a silent epidemic that has not yet attracted major. Most recently, the World Health Assembly (WHA) passed a resolution on oral health for the first time in 25 years. [World Health Organization,2007] The World Health Assembly is the supreme decision-making body for WHO and resolutions encourage Member States to adopt and implement policies. The WHA60 Resolution in 2007 emphasises the need for framing policies and strategies for oral health in the 21st century, also with the intention of oral cancer prevention and control. The statement on oral cancer reads as follows. [World Health Organization.2005]

Mechanisms of Oral Cancer Formation

Similar to the well-established colorectal carcinoma model, oral cancer is also considered to be a multi-hit process involving a number of aberrant genetic events culminating in malignant transformation at the molecular chemical and biological levels. It is known that following the action of various carcinogens (chemical, physical, biological) on normal cells in humans, a long period of several months to years (~10 months to 30 years) occurs between the development of precancer cells and their transformation into cancer cells. However, the molecular and biological events that take place within the precancer cells during this quiescent stage are not yet fully understood. Recent studies revealed that preneoplastic cell development and transformation into cancer cells is determined initially by genetic changes (oncogenes, antioncogenes), with sequential multiple somatic mutations, and later by epigenetic or environmental cell factors such as hormones, growth factors, cytokines, vitamins, and prostaglandins. These factors can markedly change the evolution of preneoplastic cells by enhancing, retarding, or inhibiting their transformation into cancer cells, or even reversing them to a normal phenotype.[33]These effects act on DNA, RNA, and protein synthesis, as well as on cell replication, cell cycles, cell surfaces, and intercellular communication. Therefore, these abnormal DNA, oncogenes or tumor suppressor genes, and ultrastructural intracellular or cell surface antigenic determinants as potential biomarkers are essential for early detection of preoralcancerus cells.

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Mechanism of Carcinogenesis

The development of oral cavity is a multistep progression that involves changes in genes related to specific genes, epigenetic events, and signal transduction within the cell [34]. Tobacco smoke contains agents that may act as mutagens. Also, tobacco smoke extract has been shown to activate the epidermal growth factor receptor (EGFR) in vitro and EGFR activation has been shown, in turn, to increase the production of prostaglandins, including PGE2 which may act in a positive feedback fashion by increasing EGFR signal transduction. Cyclin-D1 is frequently over expressed in head and neck cancer and increased cyclin-D1 activity is a downstream event triggered by EGFR activation [35]. An important epigenetic event in the progression to cancer is the silencing of gene promoter regions through hypermethylation [36], which has been shown to affect of the tumor suppressor's p16, DAP-kinase, and E-cadherin. Also, the gene for retinoic acid receptor-beta (RAR-beta) is silenced by methylation of its promoter[37]. In addition to deletions or mutations of individual genes, evidence exists demonstrating that numeric chromosomal imbalances, known as aneuploidy, may be a cause rather than a consequence of malignant transformation [38]. Aneuploidy may occur as a result of mutations in genes controlling chromosome segregation during mitosis and centrosome abnormalities.

Oral Cancer: Early Clinical Diagnosis and Staging

Primary care dental and general practitioners should play a major role play in referring patients to oral cancer treatment facilities for early diagnosis and treatment of oral cancer. Improving the skills of these primary care doctors is essential to improving prospects for early diagnosis, particularly among patients who use tobacco or alcohol in any form. Routine biopsy in those clinically presenting the oral cancer with features of oral precancerous lesions may lead to early diagnosis of underlying preclinical Investigation of oral cancer. In addition to history, physical examination, and biopsy, a simultaneous assessment of the upper aero digestive tract is necessary because patients with oral cancer have a oral cancer cell development. high risk of cancers developing in other head and neck sites and in the lungs.[39]. Oral biopsy specimens can be affected by a number of arti facts resulting from crushing, fulguration, injection, or incorrect fixation and freezing.[40]

Management of Oral Cancer Patients

While an exhaustive discussion on the management of oral cancer and precancerous lesions of oral cancer is not intended in this review, it is generally recommended that leukoplakias exhibiting degrees of epithelial dysplasia equal to, or worse than, moderate epithelial dysplasia be removed completely when possible [41]. Up to 15 percent of individuals with oral cancer harbor a second primary, making a complete head and neck cancer examination that includes the larynx imperative [42]. Surgery and radiation therapy remain the gold standards for treatment of oral cancer of the lip and oral cavity. Oropharyngeal cancer may be treated with surgery and radiation therapy for early-stage disease. For advanced-stage disease, surgery with adjuvant radiation therapy may be indicated, although recent evidence suggests that the addition of chemotherapy to radiation therapy may provide a survival advantage over radiation therapy alone in this population [43]. Patients with invasive oral cancer are best managed by a coordinated, multidisciplinary team of health care professionals, which may include a head and neck surgeon, oral and maxillofacial pathologist, general pathologist, radiation oncologist, neuroradiologist, reconstructive surgeon, medical oncologist, general dentist, oral and maxillofacial surgeon, maxillofacial prosthodontist, dental hygienist, nurse specialist, speech pathologist, nutritionist, and tobacco cessation counsellor [44].

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Treatment

Oral cancer treatment are mainly 3 types

1) Surgery
2) Radiation
3) Chemotherapy

In general, single modalities are more commonly used in earlystage SCC (Stages I & II) and carcinoma-in situ (CIS), while patients with advanced disease (Stages III & IV) are treated with a combination of therapies. [45] The type and extent of treatment are determined by factors associated with the tumour, the patient, and the medical team. [46] Tumour characteristics such as site, proximity to bone, the depth of invasion, and stage (tumour size, lymph node involvement, and risk of metastasis) are considered along with the age of the patient, co-morbidities, compliance to treatment, and the desire to make lifestyle changes.[47] Expertise of the medical team will also influence the treatment decision. [48] The likelihood of treatment side effects, both short term and long term, and how they may affect the quality of life for the cancer survivor also impact any final treatment and decision of oral cancer [49]

1. Surgery

Surgery is the most common treatment for oral cancer.[50] For more advanced tumours surgery is combined with local radio therapy and systemic chemotherapy.[51] The intent of surgery is to completely remove cancerous tissue, leaving histologically normal tumour margins while attempting to preserve normal tissue and function. [52] Surgical techniques vary as a result of access and the size of the lesion to be excised. Ideally the surgeon can excise smaller tumours from within the oral cavity. However, larger tumours and those in difficult-to-access sites may require an approach from outside the oral cavity and the removal of both soft tissue and bone. Cheek flaps may be required, either from the floor of the mouth up to access the mandible (lower cheek flap) or from below the eye and down to approach the maxilla (upper cheek flap). [53] A visor flap is when an incision is made under the chin from side-to-side and the skin is pulled up over the chin and oral cavity. [54] This technique avoids cutting the lower lip and facial aspect of the chin, while allowing for good access to the anterior aspect of the oral cavity.[55] More advanced oral cancers may involve the lymph nodes. In recent years, new technology and techniques have minimized the extent and invasiveness of surgery. [56] These efforts to reduce extensive surgery have resulted in decreased morbidity, increased function, and an overall benefit to the rehabilitation of the patient. [57]

2. Radiotherapy

New methods of drug delivery system to delivery to variation of delivery schedules. The changes were made to improve the treatment outcomes, preserve tissue, and reduce side effects of the oral cancer medicine.[58] In general, the intent of RT is to destroy DNA in dividing cancer cells in a localized region while preserving adjacent tissue and function. [59] RT as a single, primary treatment is not generally used for oral cancer, although it may be used as a sole method of treatment in cases where the location of the tumour makes it difficult to excise, such as the oropharynx, or if the patient refuses surgery [60] alone has a similar 5-year survival rate to surgery for early-stage disease, with a 37% local recurrence rate.[61] In comparison to surgery alone, radio therapy produces milder complications and offers better retention of function and aesthetics, and improved quality of life. [62] The use of surgery and postoperative RT is a common combination in oral cancer treatment, used for large tumours and when surgical margins are positive for cancer. [63] The two main types of RT are external beam radiation and brachy therapy. [64] Brachytherapy, a form of internal

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radiation, involves the precise surgical placement of a radioactive insert into the tumour, directly treating the tumour.[65] However, it is restricted by the size of the field that it can target effectively. [66] Brachytherapy can also be used in conjunction with external beam radiation. External beam radiation is provided as a daily outpatient treatment, over the course of about 6 weeks, using a linear accelerator (LINAC) that focuses radiation on the tumour site. [67] While it is a very effective cancer treatment, it also unfortunately affects the normal surrounding tissue and the normal tissue through which it travels to reach the tumour site. [68] External beam radiation is the more common form of radio therapy for the treatment of head and neck cancers. [69]

Table 2. Various Treatment Modalities for Oral Cancer

Treatment modality	**Different forms**
Surgery	Different forms Surgery Fluorescence visualization guided surgery Sentinel node mapping Laser microsurgery Reconstructive surgery TORS Cyber knife robotic radiosurgery system Osseo integrated implant surgery
Radiotherapy	Particle radiation therapy Stereotactic radiotherapy IOERT IGRT 3D conformal radiation therapy IMRT Radioimmunotherapy
Chemotherapy	Targeted therapy
Other recent developments in the treatment of oral cancer	Gene therapy Nutraceuticals

Table 2. Short- and Long-Term Effects of Oral Cancer Treatment Modalities

Treatment modality	**Short-term effects**	**Long-term effects**
Surgery	Difficulty swallowing and speaking, Anesthesia, Paresthesia	Tissue and bone loss Functional problems Cosmetic concerns Difficulty swallowing and speaking
Radiation	Mucositis, Altered taste, Decreased saliva Increased risk of infections (e.g., Candida albicans) Trismus	Xerostomia Increased risk of periodontal disease and caries Subcutaneous fibrosis Postradiation osteonecrosis Telangiectasia
Chemotherapy and targeted therapy	Nausea and vomiting leading to enamel erosion Mucositis, Skin rash, Increased bleeding	Bone marrow suppression, increasing the risk of infection Neuropathy Loss of appetite Possible renal, pulmonary, and ototoxicity
Surgery and chemoradiation	Mucositis, Stomatitis, Xerostomia, Altered taste Pain	Tissue and bone loss Increased risk of periodontal disease and caries Bone marrow suppression, increasing the risk of infection

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Table.3. Oral Chemotherapy Drugs

A	B	C	D
Afinitor (everolimus)	Bosulif (bosutinib)	Cabometyx (cabozantinib)	Droxia (hydroxyurea)
Alecensa (alectinib)		Caprelsa (vandetanib)	
Alkeran (melphalan)		Casodex (bicalutamide)	
Alunbrig (brigatinib)		Cometriq (cabozantinib)	
Arimidex (anastrozole)		Cotellic (cobimetinib)	
Aromasin (exemestane)		(cyclophosphamide caps)	
E	**F**	**G**	**H**
Emcyt (estramustine)	Fareston	Gilotrif (afatinib)	Hexalen (altretamine)
Erivedge (vismodegib)	(toremifene citrate)	Gleevec (imatinib)	Hycamtin (topotecan)
etoposide	Farydak (panobinostat) Femara (letrozole)	Gleostine (lomustine)	Hydrea (hydroxyurea)
I	**J**	**K**	**L**
Ibrance (palbociclib)	Jakafi (ruxolitinib)	Kisqali (ribociclib)	Lenvima (lenvatinib)
Iclusig (ponatinib)		Kisqali Femara Co-Pack (ribociclib and letrozole	leucovorin
Idhifa (enasidenib)			Leukeran (chlorambucil)
Imbruvica (ibrutinib)			Lonsurf (trifluridine/tipiracil)
Inlyta (axitinib)			Lynparza (olaparib)
Iressa (gefitinib)			Lysodren (mitotane
M	**N**	**O**	**P**
Matulane (procarbazine)	Nerlynx (neratinib)	Odomzo (sonidegib)	Pomalyst (pomalidomide)
Megace	Nexavar (sorafenib)		Purixan
(megestrol acetate)	Nilandron (nilutamide)		(mercaptopurine susp)
Mekinist (trametinib)	Ninlaro (ixazomib)		
mercaptopurine			
Mesnex (mesna)			
methotrexate			
Myleran (busulfan)			
R	**S**	**T**	**V**

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Revlimid (lenalidomide)	Soltamox	Tabloid (thioguanine)	Venclexta (venetoclax)
Rubraca (rucaparib)	(tamoxifen citrate)	Tafinlar (dabrafenib)	Votrient (pazopanib)
Rydapt (midostaurin)	Sprycel (dasatinib)	Tagrisso (osimertinib)	Venclexta (venetoclax)
	Stivarga (regorafenib)	tamoxifen	Votrient (pazopanib)
	Sutent (sunitinib)	Tarceva (erlotinib)	
X	**Z**		
Xalkori (crizotinib) Xatmep (methotrexate soln) Xeloda (**capecitabine**) Xtandi (enzalutamide)	Zejula (niraparib) Zolinza (vorinostat) Zykadia (cetridine)		

Traditional and Current Radiotherapy

Beam radiation, "shrinking fields" are used to deliver different doses at different regions of disease.[68] "Shrinking fields" is a technique in which the most sensitive organs are irradiated first and blocked, treating the overlying low-risk organs next with more superficial radiation.

Chemotherapy and Targeted Therapies

In the past, CT was primarily treatment of oral cancer. Innovation of new drugs, CT has a significant curative treatment in advanced oral cancer.[69] CT affects frequently dividing cells, such as those in the oral cavity, skin, bone marrow, alimentary tract, and hair follicles.[70] Current CT techniques have been shown to reduce toxicities, spare sensitive organs such as the spinal cord, optic nerve, and parotid glands, and decrease treatment time while still maintaining quality and accuracy.[71] Overall, CT offers enhanced local control, improved disease-specific survival rates and can contribute to an enhanced quality of life.[72]The delivery of CT can be divided into three categories: induction CT (before surgery), concurrent CRT (in conjunction with radiation treatment), and adjuvant CT (after surgery and/or radiation).[73] In general, the common classes of chemotherapeutic agents include platinum compounds (cisplatin and carboplatin); antimetabolites (methotrexate and 5-fluorouracil); taxanes (docetaxel); plant alkaloids; hydroxyurea; anthracyclines; and most recently taxoids. [74]

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